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Dyslipidemia and Its Association with Microalbuminuria in Children and Adolescents with Type 1 Diabetes

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ABSTRACT

Background: Type 1 diabetes mellitus (T1DM) is a chronic metabolic disorder that can lead to various complications, including diabetic nephropathy. Dyslipidemia is a common comorbidity in T1DM, and its role in the development and progression of microalbuminuria, an early marker of nephropathy, is of significant clinical interest.

Objective: Was to investigate the association between dyslipidemia and microalbuminuria in children and adolescents with T1DM.

Patients and Methods: A cross-sectional case-control study was conducted, including 60 children and adolescents with T1DM and 30 controls. Clinical and laboratory data were collected, including lipid profile, urinary albumin/creatinine ratio (A/C ratio), and other relevant parameters. Patients were divided into normo-albuminuric and microalbuminuric groups based on their A/C ratio. Statistical analyses were performed to compare the groups.

Results: Children and adolescents with microalbuminuria demonstrated significantly higher levels of total cholesterol, triglycerides, and LDL cholesterol, and significantly lower levels of HDL cholesterol compared to both normo-albuminuric T1DM patients and healthy controls.

Conclusion: Dyslipidemia is strongly associated with microalbuminuria in pediatric T1DM patients. These findings highlight the importance of early lipid management in this population to potentially prevent or delay the progression of diabetic nephropathy.

Keywords: T1DM, Microalbuminuria, Dyslipidemia, Diabetic nephropathy, Children, Adolescents.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) represents a long-term, gradually worsening condition wherein the body's own immune system mistakenly attacks and destroys the insulin-producing beta cells located in the pancreas. This autoimmune assault leads to an absolute insulin deficiency, consequently causing persistent high blood sugar levels, or hyperglycemia [1]. The long-term complications arising from T1DM are a major contributor to illness and death, significantly impairing the well-being and life expectancy of affected individuals [2]. Among these serious complications, diabetic nephropathy (DN) is a particularly concerning microvascular complication and is recognized as the primary cause of end-stage renal disease (ESRD) in individuals with T1DM[3]. The development of DN further exacerbates the health burden associated with T1DM [3].

Microalbuminuria, defined as an elevated urinary albumin excretion, is an early clinical marker of DN [4]. Early detection of microalbuminuria is crucial as it represents a window of opportunity for interventions aimed at slowing down or preventing the progression to overt nephropathy and ESRD [5]. Several factors contribute to the pathogenesis of DN, including hyperglycemia, genetic predisposition, and hemodynamic changes [6].

Dyslipidemia, a metabolic derangement characterized by the presence of abnormal concentrations of lipids, including cholesterol and triglycerides, in the blood, is a frequently observed comorbidity in individuals diagnosed with type 1 diabetes mellitus (T1DM)[7]. The typical dyslipidemic profile associated with T1DM often encompasses elevated circulating levels of total cholesterol, triglycerides (TGs), and low-density lipoprotein cholesterol (LDL-C), which is often referred to as "bad" cholesterol. Concurrently, these individuals may also exhibit decreased levels of high-density lipoprotein cholesterol (HDL-C), known as "good" cholesterol[8].

These quantitative and qualitative abnormalities in lipid metabolism are recognized to exert a significant influence on the development and subsequent progression of both macrovascular complications, affecting large arteries, and microvascular complications, affecting small blood vessels, in the context of diabetes mellitus[9]. Effectively managing dyslipidemia is therefore crucial in mitigating the long-term cardiovascular and renal risks in patients with T1DM.

The association between dyslipidemia and DN has been investigated in numerous studies [10]. Dyslipidemia can exacerbate glomerular injury and contribute to the progression of microalbuminuria to macroalbuminuria and ultimately to ESRD [11]. The mechanisms by which dyslipidemia contributes to renal damage are complex and involve several pathways, including increased oxidative stress, inflammation, and altered glomerular permeability [8].

Early identification and management of modifiable risk factors, such as dyslipidemia, are essential for preventing or delaying the onset and progression of DN

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in patients with T1DM [12]. Consequently, the primary objective of this research endeavor was to explore and delineate the association between the presence and characteristics of dyslipidemia and the occurrence of microalbuminuria in a cohort of children and adolescents diagnosed with T1DM. A specific focus was placed on elucidating the potential role of dyslipidemia as a discernible risk factor for the early stages of renal involvement, as indicated by microalbuminuria, within this vulnerable patient population[13]. Understanding this relationship could inform early identification and targeted interventions to mitigate the progression towards more advanced diabetic kidney disease in young individuals with T1DM.

PATIENTS AND METHODS

Type of study:

Cross-sectional, case-control study.

Patients:

Sixty children and adolescents suffering from type 1 diabetes for more than 3 years were included in this prospective study as the patient group. They were attending the Pediatric Department and Outpatient Clinic at the National Institute of Diabetes and Endocrinology (NIDE) during the year 2016, from 1/1/2016 to 31/12/2016. Additionally, 30 apparently healthy children and adolescents with comparable sex and age without type 1 diabetes were included as a control group.

The participants in all study groups underwent a comprehensive evaluation that included the elicitation of a detailed medical history, a thorough physical examination, precise anthropometric measurements (such as height, weight, and body mass index), and a series of relevant laboratory investigations to assess their clinical and metabolic profiles.

Inclusion Criteria:

- Type I diabetic children and adolescents diagnosed according to ADA criteria.
- Age: 4-18 years old.
- For the control group: Non-diabetic children and adolescents.
- Age: 4-18 years old.

Exclusion Criteria:

- Patients with non-diabetic renal diseases.
- Recent or ongoing acute stress.
- Pre-existing systemic inflammatory diseases or cancer.
- Concurrent use of medications other than insulin and captopril.
- (Note: Captopril use was specific to the microalbuminuria group for nephropathy treatment and wasn't a general exclusion).

METHODS

Each subject was exposed to the following:

- Full history taking with emphasis on the important relevant data.
- Thorough clinical examination including both general and systemic, with special emphasis on the following:
  - Blood pressure
  - Growth assessment by performing anthropometric measurements: including height, weight, and body mass index (BMI) which was calculated using the equation: {BMI = wt (kg) / height (m^2)}.
- Investigations included:
  - Assessment of glycemic control by assessment of HbA1c using liquid chromatographic assay method.
  - Assessment of microalbuminuria: Morning urine sample was processed and albumin in urine was measured by turbidimetric measure and creatinine by enzyme colorimetric measure, and A/C ratio was calculated.
  - A/C ratio between 30 mg/gm – 300 mg/gm is considered microalbuminuria or positive result and below this range is normoalbuminuria or negative result.
  - If the microalbuminuria is positive, it is repeated and considered positive if it is positive for 2 times in a period of 3 months with negative urinary culture.

Ethical approval:

This research protocol received approval from the Institutional Review Board (IRB) or Ethical Committee of the Faculty of Medicine for Girls, Al-Azhar University, as well as the Ethical Committee of the National Institute for Diabetes and Endocrinology (NIDE).

Prior to their children's participation, written informed consent was diligently obtained from the caregivers of all participants. This consent was secured after a comprehensive explanation of the study's nature, objectives, the potential benefits for their children and the wider community, and any foreseeable risks associated with their children's involvement in the research.

For children aged over 8 years, in addition to parental consent, informed verbal assent was also obtained. This process involved providing a simplified explanation of the study's aim and benefits in a manner understandable to them, ensuring their willing participation in the research. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Methods

The processes of data entry, processing, and subsequent statistical analysis were conducted utilizing MedCalc software, version 15.8. Parametric quantitative data were

presented as mean ± standard deviation (SD) and nonparametric as median and interquartile range (IQR). The independent t-test was used to compare the means between two independent groups, while one-way analysis of variance (ANOVA) was used to compare more than two groups.

Qualitative data were presented as frequency and were compared by Chi-Square test. P value < 0.05 was considered significant and < 0.01 was considered highly significant.

RESULTS

Table 1 compares the demographic and clinical characteristics of the control group, normoalbuminuric T1DM group, and microalbuminuric T1DM group. The microalbuminuric T1DM group showed a significantly higher mean age and MAP compared to the other groups. Z-scores for BMI, height, and weight were significantly lower in the microalbuminuric T1DM group. There was no significant difference in waist circumference between the groups. The microalbuminuric T1DM group had a significantly longer duration of diabetes mellitus.

Table 1: Demographic and clinical characteristics of participants

Variable	Control group (n=30)	Normoalbuminuric T1DM group (n=30)	Microalbuminuric T1DM group (n=30)	P value
Age (years)	14.23 ± 1.3	13.76 ± 1.27	16.2 ± 1.44	<0.001*
Gender (Female/Male)	18/12	17/13	12/18	0.251
BMI (kg/m²)	0.44 (-0.22 – 0.67)	-0.31 (-0.58 – 0.63)	-0.46 (-0.91 – 0.41)	0.02*
Height g (cm)	0.6 (0.32 – 0.82)	0.049 (-0.72 – 0.43)	-0.005 (-1.58 – 0.54)	0.001*
Weight (kg)	0.42 (0.15 – 1.05)	-0.27 (-0.87 – 0.43)	-0.36 (-1.32 – 0.43)	<0.001*
W.C (cm)	72.8 ± 5.94	70.63 ± 12.28	69.9 ± 13.16	0.568
MAP (mmHg)	81.66 ± 7.11	86.5 ± 7.7	88.41 ± 11.56	0.014*
Duration of DM (years)	-	5.41 ± 1.36	9 ± 2.06	<0.001*

Body Mass Index (BMI), Waist Circumference (W.C.), Mean Arterial Pressure (MAP), Diabetes Mellitus (DM), Significant (*). Quantitative parameters are presented as mean ± standard deviation or as median (Interquartile range). Qualitative data are presented as frequency.

Table 2 highlights the significant differences in lipid profiles among the three groups.

- Total cholesterol, triglycerides, and LDL cholesterol were progressively and significantly higher in the normoalbuminuric T1DM group and even higher in the microalbuminuric T1DM group compared to the control group ($p < 0.001$). This demonstrates a strong positive correlation between these lipid parameters and the presence and severity of microalbuminuria.
- HDL cholesterol was significantly lower in both T1DM groups (normo- and microalbuminuric) in contrast to the control group ($p < 0.001$), indicating a negative correlation with diabetic status and microalbuminuria.
- HbA1C and A/C ratio are included to show the expected differences in glycemic control and albuminuria between the groups, further contextualizing the lipid findings. The A/C ratio confirms the group classification.

Table (2): Comparison between the 3 groups concerning lipid profile data leveraging one-way ANOVA test

Variable	Control Group (30)	Normo-albuminuric DM group (30)	Microalbuminuric DM group (30)	P value
	Mean ± SD	Mean ± SD	Mean ± SD	
Lipid Profile				
Total Cholesterol (mg/dl)	128.93 ± 15.08	167.56 ± 36.9	200.7 ± 48.78	< 0.001**
TGs (mg/dl)	66.36 ± 6.01	94.13 ± 8.63	134 ± 9.39	< 0.001**
HDL Cholesterol (mg/dl)	58.13 ± 7.99	48.8 ± 11.13	46.6 ± 8.54	< 0.001**
LDL Cholesterol (mg/dl)	80.23 ± 14.79	106.16 ± 21.45	124.36 ± 4.83	< 0.001**
Related Laboratory Data				
HbA1C (%)	5.2 ± 0.4	7.5 ± 1.4	9.8 ± 2.1	< 0.001**
A/C ratio (mg/g)	8.5 ± 2.1	15.2 ± 1.1	55.4 ± 2.2	< 0.001**

Glycated Hemoglobin (HbA1C), Triglycerides (TGs), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Albumin-to-Creatinine Ratio (A/C ratio), Significant (*).

DISCUSSION

This study primarily aimed to elucidate the association and connection between dyslipidemia and microalbuminuria in a pediatric and adolescent cohort with T1DM. The findings of this investigation underscore notable disparities in lipid profiles across the examined study groups, with a particularly salient association identified between the presence of dyslipidemia and the occurrence of microalbuminuria.

The results obtained herein indicate that children and adolescents exhibiting microalbuminuria present with a significantly less favorable lipid profile when compared to their counterparts with normoalbuminuria and healthy control subjects. Specifically, the microalbuminuric group demonstrated statistically significant elevations in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels. These observations align with prior research endeavors that have established a correlation between dyslipidemia and the early stages of renal impairment in individuals with T1DM **(10,14,15)**. The consistency of these findings across different studies reinforces the potential role of dyslipidemia as an early indicator and contributing factor to the development of diabetic kidney disease in this population.

Furthermore, the study revealed a significant decrease in HDL cholesterol levels in both the microalbuminuric and normoalbuminuric T1DM groups in comparison with the control group. Low levels of HDL cholesterol are known to be an independent risk factor for cardiovascular and renal complications in diabetic patients [16,17]. The altered lipid metabolism in T1DM, characterized by increased pro-atherogenic lipids and decreased protective lipids, likely is vital to the development of diabetic nephropathy.

The mechanisms underlying the association between dyslipidemia and microalbuminuria are complex and multifactorial. ***Kasia*** **and Idogun** [18] suggested that dyslipidemia can contribute to glomerular injury by promoting oxidative stress and inflammation within the kidney. Elevated levels of LDL cholesterol can undergo oxidation, and these oxidized lipoproteins can accumulate in the mesangium, leading to cellular dysfunction and increased permeability of the glomerular filtration barrier [19].

Additionally, ***Navarro-González*** **and Mora-Fernández** [20] highlighted the role of altered lipid metabolism in the activation of various signaling pathways that contribute to extracellular matrix expansion and fibrosis in the kidney. This process ultimately leads to the development and progression of microalbuminuria.

Our findings are in agreement with the study conducted by **Thomas *et al.*** [21], which demonstrated that early lipid abnormalities can serve as significant predictors for the future development of diabetic nephropathy in patients with type 1 diabetes mellitus (T1DM). Their research supports the idea that dyslipidemia may play a contributory role in the pathophysiological mechanisms leading to renal impairment in diabetic individuals. In light of these observations, our study reinforces the necessity for routine lipid profile assessments during the early stages of T1DM, particularly in children and adolescents. Implementing timely lipid screening and appropriate therapeutic interventions could be instrumental in identifying at-risk individuals and reducing the long-term burden of renal complications associated with T1DM.

Conversely, some studies have shown conflicting results. **Mohammedsaeed and Binjawhar** [14] suggested that while dyslipidemia is common in T1DM, its direct causal role in the initiation of microalbuminuria may be less pronounced than other factors such as glycemic control and genetic predisposition. However, our study, in agreement with **Hussain et al.** [22], emphasizes that despite the possible occurrence of other risk factors, dyslipidemia significantly contributes to the severity of renal involvement.

It is pertinent to acknowledge the inherent limitations associated with the cross-sectional design leveraged in this study. This methodological approach precludes the definitive establishment of a causal nexus between dyslipidemia and the subsequent development of microalbuminuria. Consequently, future research endeavors employing longitudinal study designs are imperative to corroborate the temporal sequence of these events and to rigorously evaluate the potential impact of lipid-modifying interventions on renal outcomes within this specific patient population[23]. Such prospective investigations would provide a more robust understanding of the dynamic interplay between lipid metabolism and early renal involvement in children and adolescents with T1DM.

Despite these limitations, our study provides valuable insights into the close association between dyslipidemia and microalbuminuria in young individuals with T1DM. The results emphasize the need for aggressive lipid management strategies as part of a comprehensive approach to prevent or postpone the advancement of diabetic nephropathy in this vulnerable population [24].

CONCLUSION

This investigation compellingly demonstrates a robust association between the presence of dyslipidemia and the occurrence of microalbuminuria in children and adolescents diagnosed with T1DM. Specifically, the presence of elevated total cholesterol, LDL-C, and triglyceride levels, often accompanied by reduced HDL-C concentrations, exhibits a statistically significant

relationship with the early manifestations of renal involvement in this vulnerable patient group. These findings underscore the potential utility of lipid profile assessment as an indicator of early renal risk in young individuals with T1DM.

These findings underscore the importance of early and effective lipid management to potentially reduce the risk of diabetic nephropathy in this population.

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